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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/030,417	08/14/2002	Rainer H Muller	668-59190	8775

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EXAMINER	
EBRAHIM, NABILA G	

ART UNIT	PAPER NUMBER
1618	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/030,417	MULLER ET AL.	
	Examiner	Art Unit	
	NABILA G. EBRAHIM	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 August 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18,20, 24-34, and 38-47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18,20,24-34 and 38-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/10/2009 has been entered.

Status of Claims

Claims 1-18,20, 24-34, and 38-47 are pending in the application.

Status of Office Action: Final.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-18,20, 24-34, and 38-46 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The specification supports that the water in which the solid particles are suspended at temperature 20°C. However, there is not support for a temperature below 20°C. In accordance with MPEP 714.02 applicants

should specifically point out support for the generic concept of claim 1 using the expression "temperature below 20°C". This is a new matter rejection.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

In view of amending the claims to include "temperature below 20°C", the rejection of claims 1-4, 7, 10, 11, 13, 15, 24 and 27 remain rejected under 35 USC l02(b) as anticipated by Muller et al US 5,858,410 (Muller) is herein withdrawn.

Note that Applicant should point out support for said amendment.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-18, 20, 24-34, and 36-47 remain rejected under 35 U.S.C.103(a) as being unpatentable over Desai et al WO 98/14174 in (Desai) view of Muller US 5, 858, 410 (Muller).

Desai et al (Patent WO '174) discloses a process for preparation of microparticles or nanoparticles of water insoluble drugs; e.g. paclitaxel, an agent that is insoluble in water and uses polymers such as polylactides and polyglycolides. The drug is dissolved in an organic solvent (page 17, lines l 5-25), a protein such as albumin is added to stabilize the nanoparticles (page 17, lines 31-34) and the mixture is homogenized under high-pressure homogenization (page 18, lines 6-15 and page 51, lines 25). In disclosing a method for making a pharmaceutically acceptable formulation, Desai discusses sterile-filtration and how drug of particle size less than 200 nm is

obtained (page 19, lines 1-16, page 10, lines 24 and page 20, and lines 30-35). The drug particles can be in crystalline or amorphous for (page 13, lines 5-10); details of how to make drug particles of size less than 200 nm are provided. Furthermore, Desai et al also disclose the effect the solvent used has on drug particle size (page 38, lines 5-20) and further discuss the advantage of making the composition in the form of albumin-paclitaxel combination-low toxicity.

Regarding the amendments to the claims, the dispersion which have water-reduced dispersion medium containing less than 80 wt% of water is disclosed in Example 4 wherein the taxol is dispersed in ethanol which is free of water i.e. 0% water.

Regarding including the limitation of "at temperature of 20°C or less" would not further distinguish the instant claims over the prior art since Muller teaches suspending the particles at "room temperature" which is between 20°C to 25°C. Thus the instant claims temperature still overlap with the prior art.

Desai did not disclose the piston-gap homogenizer required in claims 44-47 Muller teaches a method for preparing nanoparticles of drugs e.g., corticoids such as prednisolone (col. 22, lines 40-45), the drug particles having average size of 10-1,000 nanometers made by dispersing solid therapeutically active drugs in a solvent and subjecting the dispersion to high-pressure homogenization in a piston-gap homogenizer (abstract and col. 20, lines 23-30) at room temperature (i.e. under 90 degrees; col. 20, lines 35-40).

Instant claims reciting "water-reduced dispersion medium containing less than 80 wt% of water", the recitation would not distinguish the instant claims over the prior art

because Muller teaches a method to make a drug carrier subjecting a solid therapeutically active compound dispersed in a solvent to high pressure homogenization in a piston-gap homogenizer to form particles having an average diameter of 40 nm to 100 nm wherein said active compound is insoluble, only sparingly soluble or moderately soluble in water, aqueous media and/or organic solvents (claim 38), note that the use of the preposition "or" means the exclusion of the aqueous media in the dispersion which is interpreted as a non-aqueous solvent and a percentage of 0% water and consequently, less than 80%. Regarding including the limitation of "at temperature of 20°C or less" would not further distinguish the instant claims over the prior art since Muller teaches suspending the particles at "room temperature" which is between 20°C to 25°C. Thus the instant claims temperature still overlap with the prior art.

The new amendments to the claim which recites "temperature below 20°C" and "water content of less than 50%" would not differentiate the claims over the prior art since the temperature as amended includes 19°C or lower which very close to room temperature of 20°C. In addition the amount of water of less than 50% is obvious over both Desai and Muller because Desai teaches paclitaxel is added to methylene chloride. The solution was added to human serum albumin solution. The mixture was homogenized for 5 minutes at low RPM (Vitris homogenizer, model: Tempest I) (Example 1). Further, Muller teaches the use of glycerol (example 4) while instant disclosure glycerol contains 0% water (see example 13, page 36 of the specification)

Therefore it would have been obvious to one of ordinary skill in the art to make paclitaxel or nanoparticles according to the methods disclosed by Desai and homogenize it in a piston-gap homogenizer because Muller teaches that it is evident that by conversion of the microparticles into nanoparticles by means of a high-energy process, to increase the surface tension to such an extent that as a result the saturation solubility increases greatly (col. 6, lines 19+). The person of ordinary skill would have expected success of having a method of preparing nanoparticles of an insoluble or barely soluble active agent using a high pressure homogenizing process in a piston-gap homogenizer and containing less than 80% of water.

Therefore the invention as a whole would have been prima facie obvious to one of ordinary skill at the time the invention was made.

Response to Arguments

Applicant's arguments filed 5/5/2009 have been fully considered but they are not persuasive.

Applicant argues that:

The solvent may be one of those of the group of water, aqueous media and/or organic solvents, but this does not automatically teach or suggest that the "homogenization solvent" should be a medium having a water content of less than 50 wt%.

To respond: Muller clearly teaches a dispersion medium having little or no water (see claims 29-33 of Muller). In addition, in Example 4 of Muller, Muller uses glycerol while

instant disclosure glycerol contains 0% water (see example 13, page 36 of the specification)

Applicant argues that

Similarly for claim 29 of Muller, there is no mention that the non-aqueous medium is the homogenization medium. The "said particles" to which this claim refers is only mentioned in claim 1, but claim 1 refers only to the product particles, i.e. after the high pressure homogenization.

To respond: The claim recites "wherein said particles are dispersed in a non-aqueous medium", if Applicant alleges that said medium is not the homogenization medium, then why Applicant does not cite or show what did the homogenization medium include?

Applicant argues that

It has to be noted that in Desai the drug is dissolved, which is contrary to the present invention in which maintains the drug in solid form.

To respond: Desai discloses that protein and pharmacologically active agent in a biocompatible dispersing medium are subjected to the homogenizer (abstract). Therefore, it is clear that the active agent is dispersed not dissolved.

Applicant argues that

Desai does not teach to use a non-aqueous homogenization medium in piston-gap high pressure homogenization or with solid drugs. Prior to the present invention, there was always use of water as homogenization medium in a piston-gap high pressure homogenization because of the cavitation effect to be used for comminution of the emulsion droplets.

To respond: Desai teaches that paclitaxel is added to methylene chloride. The solution was added to human serum albumin solution. The mixture was homogenized for 5 minutes at low RPM (Vitris homogenizer, model: Tempest I) (Example 1). Since methylene chloride is a non-aqueous liquid, then the resulting solution is non-aqueous and there is no cavitation formation (as an evidence, see Example 2 which discloses the method of cavitation formation and the high shear homogenization.)

Applicant argues that

Desai and Muller teach away because both references teach imparting high shear and cavitation.

To respond: avoiding cavitation is not specifically recited as an active step in the claims, but only recited as a result of the homogenization process. Since the prior art teaches the same process, the same result thereof would be expected to occur. The claims as written do not specifically exclude cavitation in the process as argued by applicant. Further, Muller teaches using cavitation or shearing and impact forces with introduction of a high amount of energy (Summary). Thus, Muller teaches a method that excludes cavitation.

Applicant argues that:

The experimental evidence of record rebuts any prima facie case of obviousness based on the combination of Desai and Muller. As discussed previously, Applicants have now found that during high-pressure homogenization using a piston-gap homogenizer, water vapor is created in the form of bubbles, which subsequently implode, otherwise known as cavitation. The resulting implosion shock waves lead to

particle diminution. However, many materials are destroyed, melted or otherwise undesirably altered by these violent shock waves (cavitation). Applicants have solved the problems of cavitation by providing a far more gentler method of obtaining the same particle size without using the implosion shock waves (i.e. substantially avoiding cavitation or reducing cavitation):

1) reducing or eliminating the use of water; and/or

2) reducing the temperature of the medium being homogenized.

To respond: the temperature used in Muller also overlaps with the value recited in the claims of 20°C or less. Further, the water amount is reduced or avoided since Muller discloses drug carrier by subjecting a solid therapeutically active compound dispersed in a solvent to high pressure homogenization in a piston-gap homogenizer to form particles having an average diameter of 40 nm to 100 nm wherein said active compound is insoluble, only sparingly soluble or moderately soluble in water, aqueous media and/or organic solvents (claim 38). Thus water can be excluded and alternatively, organic solvents are used. Therefore, eliminating water and reducing temperature are anticipated by Muller. Further, the resulting products are the same. If Applicant believes that these two conditions would avoid cavitation, why would not Muller's method do the same?

Applicant argues that:

It is believed, without being bound to any theory, that effects other than cavitation are responsible for the observed diminution action. Contrary, to the general knowledge in the art represented by Desai and Muller, Applicants have found that cavitation is not the

dominating diminution principle in the present invention. This is further supported by performing homogenization at lower temperatures, e.g. at 20° Celsius or below. A surprisingly similar efficiency in diminution is observed, which is contrary to the general beliefs in the art.

To respond: In re Best, 195 USPQ 430, and In re Fitzgerald, 205 USPQ 594, the court discuss the support of rejections wherein the prior art discloses the subject matter, which there is reason to believe inherently includes functions that are newly cited and instantly claimed. As explained supra, Muller followed the limitations and conditions recited in the instant claims. Whatever are the results accomplished by reducing water and using lower room temperature, these should be achieved by Muller's invention. If Applicant found a new theory for explaining these results, this would not impart patentability.

Applicant argues that:

Present claims 46 and 47 recite particles of "5.6 micron or less," which are not included in Desai's particle ranges. For this reason alone, the Section 103 rejection of claims 46 and 47 should be withdrawn.

To respond: Desai discloses that the particles can be of 200 nm of diameter which is less than the recited 5.6 micron (page 10).

Applicant argues that:

Claim 25 recites carrying out the process with the exclusion of oxygen and claim 26 recites degassing the dispersion medium before use. None of the cited references teach or suggest these limitations.

To respond: instant specification at page 8 disclosing that degassing of the dispersion medium (e.g. in a vacuum or by heating). Desai teaches that solvent is rapidly evaporated under vacuum to yield a colloidal dispersion system (page 20, 31+). The reference also teaches that the volatile component may be removed by evaporation (optionally under vacuum) (page 32, lines 17+). Note that vacuuming to exclude vapors reads on degassing including oxygen.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to NABILA G. EBRAHIM whose telephone number is (571)272-8151. The examiner can normally be reached on 9:00AM - 6:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Nabila G Ebrahim/
Examiner, Art Unit 1618

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